Title

Effect of frequent hemodialysis on residual kidney function.

Journal

Kidney international, 83(5)

ISSN

0085-2538

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Publication Date

2013-05-01

DOI

10.1038/ki.2012.457

Peer reviewed

HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2013 December 07.

Published in final edited form as:

Kidney Int. 2013 May ; 83(5): 949–958. doi:10.1038/ki.2012.457.

Frequent nocturnal hemodialysis accelerates the decline of residual kidney function

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Abstract

Frequent hemodialysis can alter volume status, blood pressure and the concentration of osmotically active solutes, each of which might affect residual kidney function (RKF). In the Frequent Hemodialysis Network Daily and Nocturnal Trials, we examined the effects of assignment to 6 compared to 3 times per week hemodialysis on follow up RKF. In both trials, baseline RKF was inversely correlated with number of years since onset of ESRD. In the Nocturnal Trial, 63 participants had non-zero RKF at baseline (mean urine volume 0.76 l/d, urea clearance 2.3 ml/min, and creatinine clearance 4.7 ml/min). In those assigned to frequent nocturnal dialysis, these indices were all significantly lower at month 4 and were mostly so at month 12 compared to controls. In the frequent dialysis group, urine volume had declined to zero in 52% and 67% of patients at months 4 and 12, respectively, compared to 18% and 36% in controls. In the Daily Trial, 83 patients had non-zero RKF at baseline (mean urine volume 0.43 l/d, urea clearance 1.2 ml/min, and creatinine clearance 2.7 ml/min). Here, treatment assignment did not significantly influence follow-up levels of the measured indices, although the range in baseline

Disclosure

Dr. Chertow serves on the Board of Directors and the Scientific Advisory Board for Satellite Healthcare, Inc., and on the Scientific Advisory Board for DaVita Clinical Research. He also serves as an advisor for Hemodialysis Plus, Inc.

RKF was narrower, potentially limiting power to detect differences. Thus, frequent nocturnal hemodialysis appears to promote a more rapid loss of RKF, the mechanism of which remains to be determined. Whether RKF also declines with frequent daily treatment could not be determined.

Introduction

The goal of the Frequent Hemodialysis Network (FHN) Trials was to evaluate the safety and efficacy of 6 times per week Nocturnal (home) or Daily (in-center) hemodialysis *versus* conventional (3 times per week) hemodialysis on an array of intermediate outcomes.[1] Challenges to enrollment and randomization,[2] baseline characteristics of enrolled participants[3] and the primary results of both trials[4,5] have been published, as have selected secondary results focusing on mineral metabolism,[6] cardiac structure,[7] physical performance,[8] nutrition and body composition.[9]

While residual kidney function (RKF) was not among the nine pre-specified main outcome domains in the FHN trials,[1] there is growing interest in the effect of various dialysis treatments on the trajectory of RKF.[10] The average estimated glomerular filtration rate (eGFR) of persons initiating dialysis in the United States averaged about 10 mL/min in recent years.[11] Much of RKF is lost during the first 18 months of hemodialysis, and appears to depend on the primary cause(s) of kidney failure as well as other patient- and treatment-related factors.[12] Patients on peritoneal dialysis generally exhibit slower loss of RKF than do patients on hemodialysis,[13–17] suggesting that hemodialysis-dependent factors may contribute.[4,5] Several cohort studies have suggested that RKF is an extremely important determinant of mortality and morbidity in patients on either peritoneal dialysis or hemodialysis.[12] Frequent hemodialysis theoretically could slow or hasten progressive loss of RKF. Frequent hemodialysis combined with increased weekly treatment times typically reduces the rate of ultrafiltration during hemodialysis and lowers the frequency and severity of intradialytic hypotensive episodes per session.[4,5] Fewer episodes of intradialytic hypotension might reduce ischemic kidney injury and preserve RKF.[12] On the other hand, lower blood pressures associated with more effective and complete ultrafiltration might reduce kidney perfusion, hastening the loss of RKF.[15] A reduced need for antihypertensive medication[18,19] may lead to discontinuation of ACE inhibitors or angiotensin receptor blockers. In observational studies, use of ACE inhibitors and angiotensin receptor blockers has been associated with preservation of RKF.[14] Frequent hemodialysis may dilute the concentration of potentially toxic retained uremic solutes, but may also lower concentrations of osmotically active solutes (such as urea) that may help maintain urine flow rate and GFR.

In considering these competing potential effects, we hypothesized that frequent hemodialysis would result in more rapid decline in RKF, as measured by 24-hour urine volume (UVol), and kidney urea (Kru) and creatinine (Krcreat) clearances.

Results

Residual Kidney Function at Baseline

Tables 1 and 2 present baseline characteristics of participants with zero Uvol (left side) and of participants with nonzero Uvol grouped according to randomized treatment assignment (right side). In the Nocturnal Trial, the 63 of 87 randomized participants with nonzero baseline Uvol had a mean 24-hour UVol of 0.76 L/d, Kru 2.3 mL/min, and Krcreat 4.7 mL/min. In the Daily Trial, the 83 of 245 randomized participants with nonzero baseline UVol had mean UVol 0.43 L/d, Kru 1.2 mL/min, and Krcreat 2.7 mL/min.

At baseline, ESRD vintage was inversely correlated with UVol (Figure 1 and Tables 1 and 2). In the Nocturnal Trial, mean ESRD vintage in those with zero urine output was 6.14 years, while in those with nonzero output it was 2.42 years (Table 1). In the Daily Trial, ESRD vintages for zero and nonzero urine output averaged 7.37 and 2.48 years, respectively. Blood pressure, MRI-measured left ventricular mass, MRI-measured end-diastolic volume (LVEDV), and bioimpedance-estimated extracellular water volume were not markedly different in participants without, compared to those with, urine output (Tables 1 and 2). In those participants with urine output, baseline UVol, Kru and Krcreat were directly and significantly correlated; In the Nocturnal Trial, the Spearman correlation coefficient for UVol *versus* Kru was 0.69, for UVol *versus* Krcreat was 0.53, and for Kru *versus* Krcreat was 0.90. In the Daily Trial, analogous correlation values were: UVol *versus* Kru: 0.78; UVol *versus* Krcreat: 0.59; and for Kru *versus* Krcreat: 0.79.

Treatment characteristics and drug exposures

The distributions of achieved weekly Kt/V and weekly treatment time in the two treatment arms have been summarized previously.[4,5] All dialyzers used in the FHN Trials, with two patient exceptions, were high flux, and > 95% of dialysis treatments were performed with membranes that were some combination of polysulfone, polyethersulfone, polyamide, polyarylethersulfone, or polyacrylonitrile. No more than 11% of participants used nonsteroidal anti-inflammatory drugs at any visit in either the Daily or Nocturnal Trials. In the Nocturnal Trial, the proportion of patients using ACE inhibitors or angiotensin receptor blockers changed from 45% to 46% in the conventional arm, and from 28% to 22% in the frequent arm. In the Daily Trial, the corresponding proportions decreased from 50% to 46% in the conventional arm and from 49% to 34% in the frequent arm.

Effects of Randomized Treatments

All analyses of the effect of the randomized treatments on RKF were restricted to the 63 participants in the Nocturnal Trial and 83 in the Daily Trial with nonzero RKF at baseline. In the Nocturnal Trial, 2 of 32 participants who were randomized to frequent hemodialysis died and 2 additional participants underwent kidney transplantation, compared to 1 death and 2 transplants for 31 participants randomized to conventional dialysis. In the Daily Trial, 2 of the 35 who were randomized to the frequent dialysis group died and 3 were transplanted, compared to 3 deaths and 5 transplants for 48 participants randomized to conventional dialysis. Several additional patients had missing RKF measurements due to missing or incomplete kinetic modeling information. The sample sizes for the patients with

nonmissing RKF measurements who were retained in the statistical analyses are displayed in the leftmost columns of the 4-month and 12-month portions of Tables 3 and 4.

Table 3 (Nocturnal Trial) and Table 4 (Daily Trial) display the results of the nonparametric intent-to-treat comparisons of the RKF outcomes between the randomized groups at months 4 and 12 (see methods). Figures 2 and 3 display the proportions of patients with RKF outcomes equal to 0, and the proportions falling within the three tertiles defined by the baseline distribution for each RKF parameter. Values are shown at baseline and at follow-up months 4 and 12. In each figure, UVol is shown in panel (a), Kru is shown in panel (b), and Krcreat is shown in panel (c). In the Nocturnal Trial, levels of all three of these parameters, as well as the average of Kru and Krcreat, were significantly lower for participants assigned to 6 times per week hemodialysis compared to participants assigned to conventional hemodialysis at Month 4, with this difference largely persisting at Month 12. The percent of patients with UVol equal to 0 increased from 0% at baseline to 52% and 67% at months 4 and 12, respectively, in the frequent nocturnal group, but only to 18% and 36%, respectively, at months 4 and 12, in the conventional hemodialysis group. In the Daily Trial, the levels of UVol, Kru and Krcreat were similarly distributed between the two treatment groups at both follow-up times.

Post hoc As-treated Analyses

In *post hoc* analyses, we examined the relationship between the baseline and follow-up values of UVol and each patient's average number of recorded treatments and the average weekly treatment time. As shown in Figure 4, whereas results in the Daily Trial were equivocal, in the Nocturnal Trial, 1 of 16 (6%) of participants who followed a schedule of at least 4.5 treatments per week retained some RKF by Month 12; by contrast, 17 of 25 (68%) participants with fewer than 3.5 treatments retained some RKF through Month 12 (additional details in Supplement).

Exploratory Correlational Analyses

In exploratory analyses, we examined associations of the change in UVol between baseline and month twelve with the change in each of several intermediate variables that might be considered potential mechanisms for the effect of more frequent dialysis on RKF. These included change in predialysis systolic or diastolic blood pressure, lowest intradialytic blood pressure, extracellular fluid volume, left ventricular end-diastolic volume, and osmotic load (as reflected by BUN). As shown in Table 5, changes in levels of each of these variables were not associated with change in UVol from baseline to Month 12, with one exception: in the 6 times per week treatment groups in both the Nocturnal Trial and Daily Trials, the change from baseline to early follow-up in level of minimum intradialytic systolic blood pressure was associated with decrease in Uvol at Month 12.

Discussion

In the FHN Nocturnal Trial, assignment to frequent hemodialysis was associated with a more rapid decrease in residual kidney function (RKF) whether the chosen RKF metric was urine volume, urea clearance, or creatinine clearance. This effect was apparent by 4 months

after randomization and remained evident after 12 months. In the Daily Trial, where the maximum allowed baseline level of RKF was lower by design (Kru <3 mL/min per 35L estimated body water volume), treatment assignment to frequent hemodialysis did not significantly influence the change in RKF.

As reviewed by Vilar and Farrington,[10] RKF is associated with improved survival in patients on peritoneal- and hemodialysis,[20–26] and also with lower hospitalization rates,[27] better nutrition, [25,28–30] less anemia and improved control of serum phosphorus.[31,32] Also, substantial RKF has been associated with lower plasma concentrations of so-called “middle molecules”,[33,34] better control of hypervolemia and hypertension[25,35] and reduced left ventricular hypertrophy.[36] It is therefore of some concern that despite some important observed benefits, participants randomized to 6-times per week hemodialysis in the Nocturnal Trial showed a more rapid decline in RKF compared to participants on conventional thrice weekly hemodialysis.

RKF may not be constant throughout the interdialytic interval. For example, Van Olden et al. showed that in 3 times per week hemodialysis,[37] when RKF was assayed on successive days of the interdialytic interval, GFR progressively increased. The presumed drivers for this variation include the progressive increase in volume and solute load as the interdialytic interval progresses. In the FHN Trials, most urine collections occurred towards the end of interdialytic intervals. Therefore, in the participants dialyzed 3 times per week, the urine collection period usually did not extend for the entire interdialytic interval, while in the participants dialyzed 6 times per week, when urine collection was done midweek, the entire interdialytic interval was sampled. Thus, in the participants dialyzed 3 times per week, urine collections may have overestimated the average RKF relative to participants dialyzed 6 times per week due to this sampling bias. However, when RKF drops to zero, such potential sampling bias is no longer an issue; in the Nocturnal Trial at 4 months, a higher fraction of participants randomized to 6 times per week therapy had zero RKF compared to controls. In those participants in whom urine output did not drop to zero, some possibility for bias still exists. However, a sensitivity analysis described in the Supplemental Materials suggested that differences in urine collection periods between the 3 and 6 times per week arm were not likely to be responsible for the apparent adverse treatment effect of 6 times per week hemodialysis on RKF.

Intradialytic hypotension has been proposed as a possible cause of accelerated loss of RKF with conventional hemodialysis.[12] Kidneys of patients with CKD have a diminished capacity to autoregulate, and hence may be susceptible to ischemic damage due to transient drops in blood pressure during dialysis. We previously reported that in the FHN Nocturnal Trial, the proportion of sessions complicated by intradialytic hypotension requiring intervention was reduced in participants randomized to the 6 times per week dialysis,[5] suggesting that intradialytic hypotension could not be a likely explanation for more rapid loss of RKF; however, in both the Nocturnal and Daily Trials, the decrease from baseline to early follow-up in the minimum systolic blood pressure recorded during dialysis was associated with the decrease in urinary volume from baseline to Month 12. Therefore, a blood pressure-related mechanism for the accelerated fall in RKF cannot be entirely discounted.

There are a number of possible reasons why RKF might decrease more rapidly with frequent nocturnal hemodialysis. RKF may be sustained in part by a relatively expanded extracellular fluid volume,[38] often accompanied by hypertension.[15,39] An osmotic diuresis induced by retained small molecular weight solutes may drive RKF and result in increased UVol. With frequent hemodialysis, each of these three drivers of RKF (extracellular volume, blood pressure, and osmotic load) may potentially be reduced. In our study, the associations among changes in each of these putative "mechanistic" factors and change in UVol were examined, and no clear cut relationships were found. The use of ACE inhibitors or angiotensin receptor blockers decreased slightly in the frequent dialysis arms of both trials. Because ACE inhibition has been associated with prolonged RKF in some studies, it is possible that stopping ACE inhibitors might have played a role in accelerated loss of RKF in some patients, but sample sizes were too small to explore this possibility.

Another possible reason for accelerated loss of RKF with frequent nocturnal hemodialysis concerns platelet activation and an increased inflammatory response. As blood courses through the extracorporeal circuit, platelet activation increases, platelet-platelet and platelet-leukocyte aggregates form that may lodge in tissues, causing inflammatory and oxidative tissue damage, including to the kidneys.[40] When hemodialysis is utilized 7–8 hours per session 6 times per week, this blood-to-circuit contact activation process is occurring up to 48 hours per week.

Almost all patients in the two FHN trials were being dialyzed with high-flux membranes. The total use of "cellulosic" membranes was < 5%, and most of the cellulosic membranes used were cellulose triacetate, which is believe to be a relatively biocompatible surface. In the Nocturnal Trial, most of the patients were dialyzed at home in both arms. As described in Methods, an ultrafilter was used for final purification of product water, and no differences were found in endotoxin levels in either product water or dialysate between the two treatment arms.

Post hoc as-treated analyses relating UVol to the actual recorded average number of weekly treatments and weekly treatment time provided further evidence of a reduction in RKF with frequent nocturnal dialysis. In the Nocturnal Trial, all but one patient who complied with the more frequent dialysis prescription lost all RKF by Month 12 (Figure 4). As-treated results should always be interpreted with caution, as there always is a risk of selection bias; specifically, in this instance, patients who had lost RKF might have been more adherent with more frequent dialysis due to subjective clinical improvement, or greater perceived freedom to ingest salt and water. Nevertheless, an alternative explanation might be that frequent nocturnal hemodialysis as performed in the Nocturnal Trial was truly deleterious.

Might frequent hemodialysis be performed in such a way as to minimize loss of RKF? For example, in patients with substantial RKF, blood and dialysate flow rates could be reduced to avoid excessively low blood urea nitrogen concentrations. The intensity of sodium restriction typically recommended to patients on conventional hemodialysis could be somewhat liberalized, so as to avoid intradialytic or interdialytic volume depletion. One recent intervention in this particular direction, however, was unsuccessful, with 10 of 18 of patients withdrawing from the study because of adverse events.[41] Techniques to minimize

platelet activation during dialysis might reduce this process and help preserve RKF. While use of more "biocompatible" synthetic membranes may reduce platelet activation,[42] in the FHN trial, membranes largely believed to be biocompatible were used. Studies to examine the effect of "anti-platelet-activating" drugs on RKF may also be of interest.

While more frequent hemodialysis may hasten the fall in RKF, other salutary effects of frequent hemodialysis could counterbalance this effect. Although mortality and hospitalization outcomes have not yet been assessed in adequately powered randomized controlled trials, frequent nocturnal hemodialysis *per se* has been shown to lower plasma levels of beta-2-microglobulin, protein-bound toxins, and phosphorus. Frequent nocturnal hemodialysis also has been reported to result in partial correction of left ventricular hypertrophy,[18,19,43,44] although results from several trials including the FHN Nocturnal Trial, are mixed.

This study has several strengths. First, results were derived from two randomized clinical trials. Second, we objectively assessed RKF using three complementary and well validated metrics, UVol, Kru and Krcreat. Third, while the trial populations were selected, there was broad representation by age, sex, race/ethnicity, ESRD vintage and primary cause of kidney disease.[2,3] This study also has several limitations. The design of the Daily Trial was not conducive to addressing the question of whether 6 times per week therapy reduced RKF in a similar fashion to what we observed for nocturnal dialysis. A large fraction of participants in the Daily Trial had zero UVol and could not be assessed for change over time. Moreover, the range of RKF (as gauged by Kru) was narrow, as patients with Kru >3 mL/min/35L estimated body water were excluded from participation. Thus, while the Daily Trial reached 98% of its recruitment target, its power to detect a treatment-related change in RKF was limited. Although the Nocturnal Trial had more difficulty in recruitment, a much larger fraction of participants had nonzero UVol, and could be assessed for changes in UVol, Kru and Krcreat. Finally, the study was not blinded (due to the nature of the intervention). Since participants were not directly observed during their timed urine collections, the completeness of collection may have been influenced by the group to which each subject was randomized.

In summary, frequent nocturnal hemodialysis appears to accelerate loss of RKF. We were unable to properly evaluate whether a similar adverse effect on RKF occurs with the more commonly prescribed "short daily" dialysis type of schedule that was used in the Daily Trial. Given the strong associations among RKF, mortality and morbidity in peritoneal and hemodialysis cohorts, the potential for more rapid loss of RKF should be considered when balancing the risks and benefits of frequent hemodialysis in individual patients.

Methods

The Frequent Hemodialysis Network (FHN) Daily Trial was a multi-center, prospective, randomized, parallel-group trial of frequent (6 times per week), as compared with conventional (3 times per week) in-center hemodialysis.[1] The FHN Nocturnal Trial was a similarly designed trial comparing the effects of frequent (6 times per week) with conventional (3 times per week) nocturnal hemodialysis.[1] The majority of participants in the

Nocturnal Trial were receiving hemodialysis at home, with only the 6 times per week participants receiving hemodialysis at night. Detailed description of study designs have been previously described.[1]

Subjects on maintenance hemodialysis needed to achieve a mean equilibrated Kt/V_{urea} >1.0 for the last two baseline hemodialysis sessions. Major exclusion criteria included age <13 (Daily) or <18 (Nocturnal) years, KrU >3 mL/min/35L (Daily) or residual GFR (mean of creatinine and urea clearance) >10 mL/min/1.73m^2 (Nocturnal), life expectancy <6 months, medical need for hemodialysis >3 times per week, history of poor adherence to hemodialysis, and anticipated kidney transplant or relocation within 12 months. Informed consent was obtained from each subject. The trials were approved by the Institutional Review Board at each participating study site and conducted in full accordance with the Declaration of Helsinki.

After randomization in the Nocturnal Trial, participants were assigned to either 3 times per week hemodialysis to a prescribed standard Kt/V_{urea} of >2.0 and a session length of ≥ 2.5 hours or 6 times per week hemodialysis to a standard Kt/V_{urea} of ≥ 4.0 for ≥ 6 hours per session. After randomization in the Daily Trial, participants who were assigned to hemodialysis 6 times per week (n=125) had a target equilibrated Kt/Vn (where $Vn=3.271\times V^{2/3}$) of 0.9 provided that the length of the session was between 1.5 and 2.75 hours.[21] Subjects who were assigned to 3 times per week hemodialysis continued their usual hemodialysis prescriptions, which included a minimum target equilibrated Kt/V_{urea} of 1.1 and a session length of 2.5 to 4.0 hours.

All laboratory measurements were performed by local laboratories. Blood was drawn either as serum or plasma, centrifuged, and then the refrigerated sample was sent to the local laboratory for analysis within 24 hours. Bioimpedance measurements (midweek, predialysis) were performed by study coordinators trained in the use of the device.[9] Measurements of resistance and reactance were done with a single-frequency (50 kHz) wrist-to-ankle bioimpedance analysis device (RJL Systems, Clinton Township, MI, USA). Extracellular volume was calculated as the difference between total body water[45] and intracellular volume.[46]

Timed 24 hour urine collections were performed during the interdialytic intervals preceding kinetic modeling sessions for patients producing at least 80 ml of urine/24 hrs at baseline, Month 4 and Month 12 of follow-up (additional details in Supplemental materials). For each of these kinetic modeling sessions a 2-pool urea kinetic model was fit to estimate the patient's 2-pool urea volume (Vdp) based on the pre and post dialysis BUNs, the dialyzer clearance computed from blood flow, dialysate flow and dialyzer K_0A, and the patient's recorded treatment schedule of the week preceding the modeling session. The Runge-Kutta algorithm was used to estimate the patient's BUN vs. time concentration curve over the full week, including the time period during which the urine collection was performed. An intercompartmental urea clearance (Kc, ml/min) of 0.016 × Vdp (Vdp = 2-pool urea distribution volume in mL) was assumed to account for post-dialysis rebound. The estimated Vdp was then used as an input parameter in to fit an analogous 2-pool kinetic model to the pre- and post-dialysis serum creatinine concentration, solving for the dialyzer clearance of

creatinine and the creatinine vs. time concentration curve over the same week. A creatinine Kc of 0.010 × Vdp was assumed. Finally, residual urea and creatinine clearances were estimated as the excretion rate of each solute divided by the time-averaged serum concentration of each solute during the collection period. The latter was estimated from the weekly serum urea and creatinine profiles generated by 2-pool kinetic modeling.

In two cases, missing post-dialysis BUNs or post-dialysis creatinine were imputed by multiplying the pre-dialysis BUNs and pre-dialysis creatinines by the average post vs. predialysis BUN or creatinine ratios from neighboring kinetic modeling sessions 1 month prior to and 1 month after the kinetic modeling session with the residual urine collection. In 4 other cases in which urine collections were performed outside of the week prior to the kinetic modeling session, the time averaged urea and creatinine concentrations were imputed by treating the collection as though it occurred in the interdialytic interval preceding the kinetic modeling session, with the same time between the collection and the initiation of the kinetic modeling session as the time between the collection and the subsequent dialysis after the after urine collection. Residual GFR (in ml/min) was estimated as the average of the residual urea and creatinine clearances.

Data Analyses

Baseline characteristics were summarized as frequency and percent for categorical variables and as means and standard deviations for continuous variables, with patients grouped into those with 0 RKF (operationally defined as those producing < 80 ml of urine volume/24 hr), and those with nonzero RKF. Scatter plots with local regression curves were used to relate UVol to ESRD vintage at baseline.

Prior to examination of outcome data, the study investigators designated UVol as the main secondary outcome for the RKF domain, while residual urea clearance, residual creatinine clearance, and residual GFR were designated as additional secondary outcomes. All outcome analyses were restricted to patients with non-zero RKF at baseline. The main intent-to-treat analyses compared the 4-month and 12-month values of each of the four RKF outcomes between the randomized treatment groups using a nonparametric Wilcoxon rank sums test, with stratification by the tertiles of the baseline level of the outcome being analyzed. The Van Elteren version[47] of the stratified Wilcoxon test was used as implemented in the FREQ procedure of SAS. Results of the intent-to-treat comparisons of each of the above outcomes were also graphically displayed at months 4 and 12 by stacked bar-charts, showing the % of patients with 0 RKF and the % falling within each of the three tertiles of the baseline level of the RKF outcome. Sensitivity analyses were performed to investigate the dependence of the study results on differences in the timing of the urine collections in the interdialytic intervals between the study groups (see Supplementary Materials).

We also displayed the relationship of the changes in UVol from baseline to months 4 and 12 with the average number of recorded treatments per week and with the average recorded weekly treatment time over the preceding follow-up months. Spearman correlations were used to summarize the association of changes in UVol from baseline to 12 months with changes in other parameters.

All analyses were performed without formal adjustment for multiple comparisons using SAS version 9.2. Two-tailed *P* -values <0.05 were considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Supported by the National Institutes of Health (NIH), National Institutes of Diabetes and Digestive and Kidney Diseases, the Center for Medicare and Medical Services, and the NIH Research Foundation. Contributors to the NIH Foundation in support of the FHN trials included Amgen, Baxter, and Dialysis Clinics, Inc. (DCI). Additional support was provided by DaVita, DCI, Fresenius Medical Care, Renal Advantage, Renal Research Institute, and Satellite Healthcare. A list of members of the FHN Trial Group for each study has been published in references 4 and 5.

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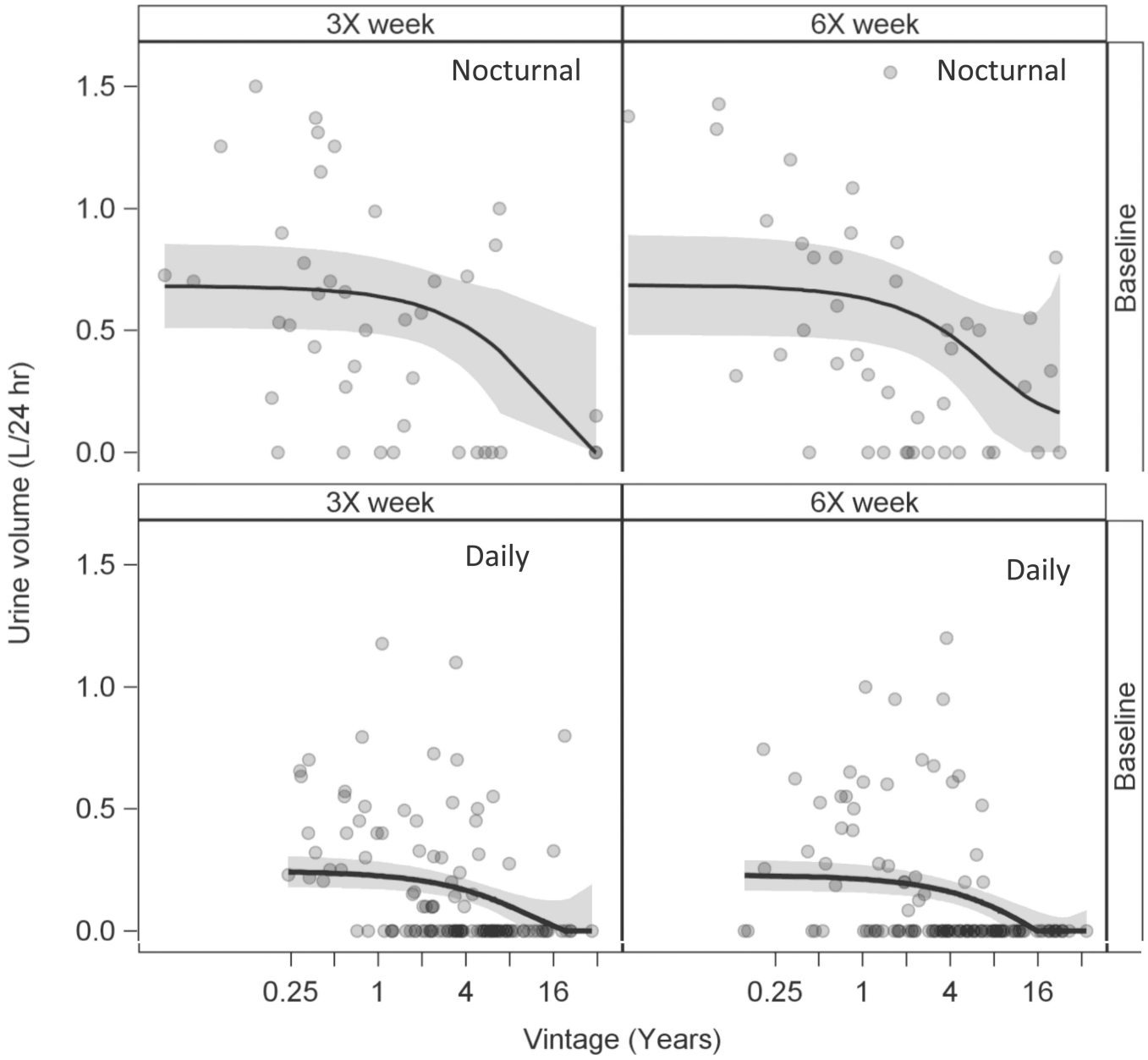
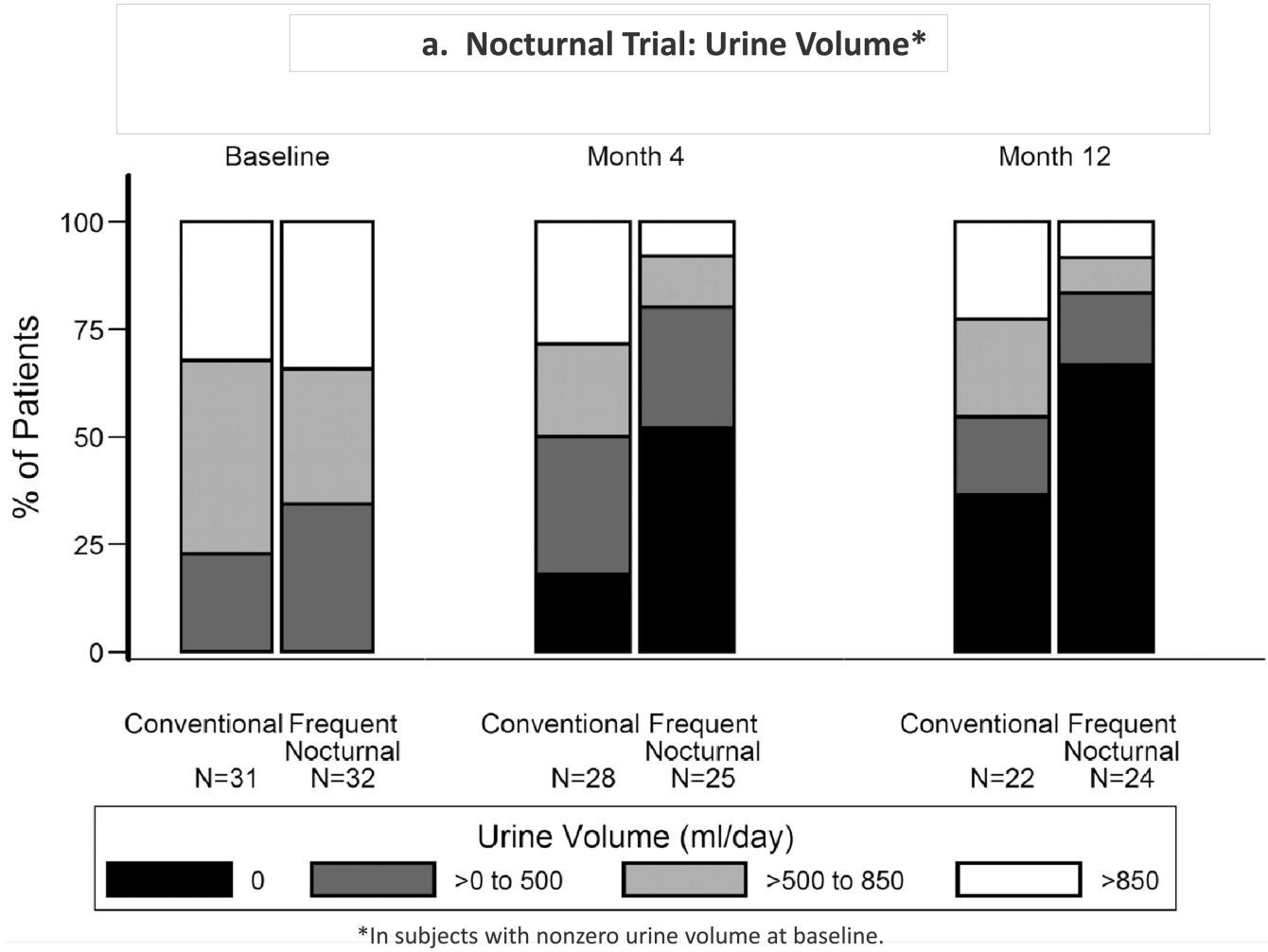
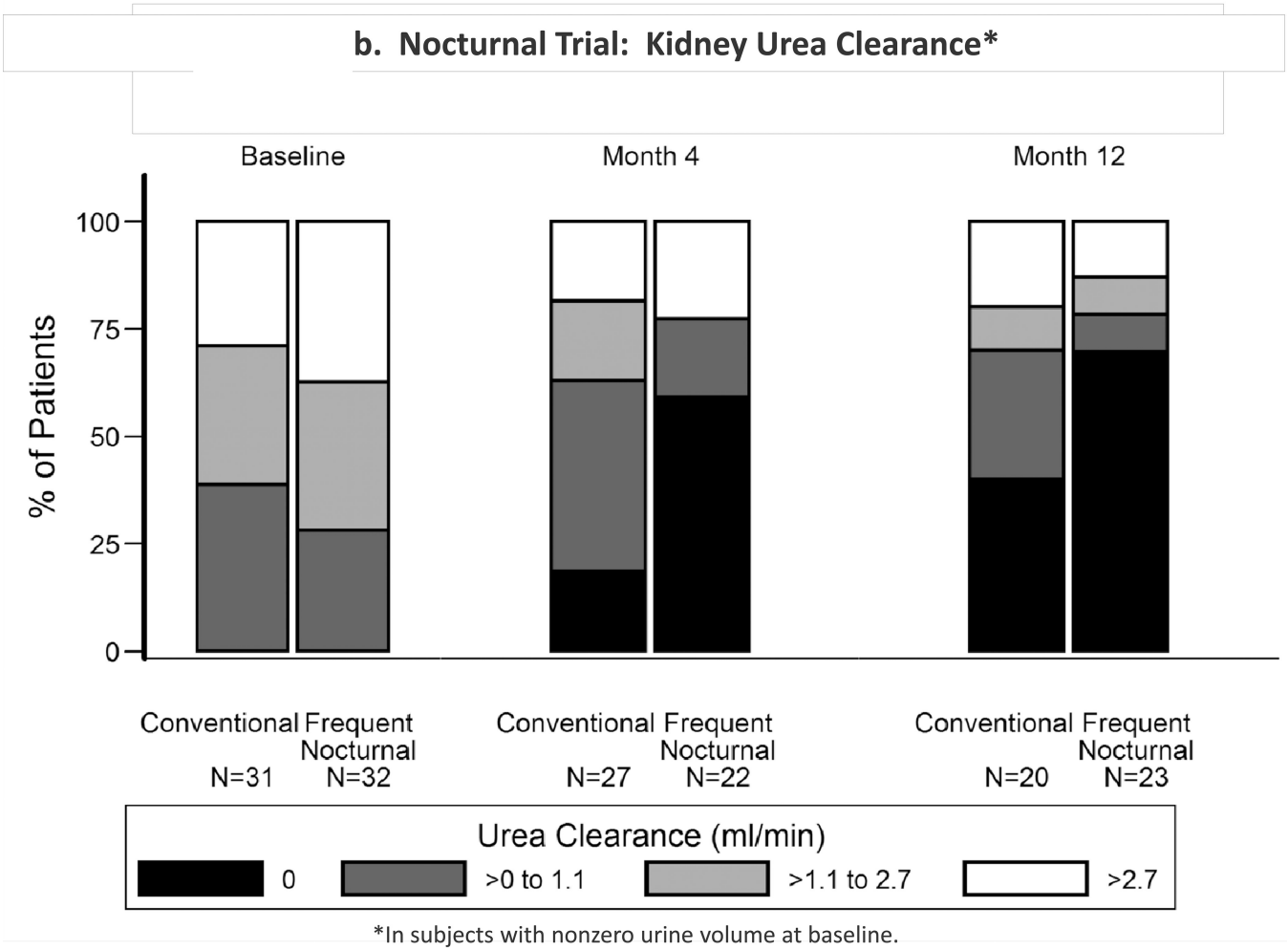


Figure 1.

Regression analysis of baseline urine volume as a function of ESRD vintage for the Nocturnal and Daily Trials. The drawn curves were fit using locally weighted least squares regression. The Spearman correlations between vintage and baseline urine volume were −0.49 ($p < 0.0001$) in the Daily Trial, and −0.53 ($p < 0.0001$) in the Nocturnal Trial.





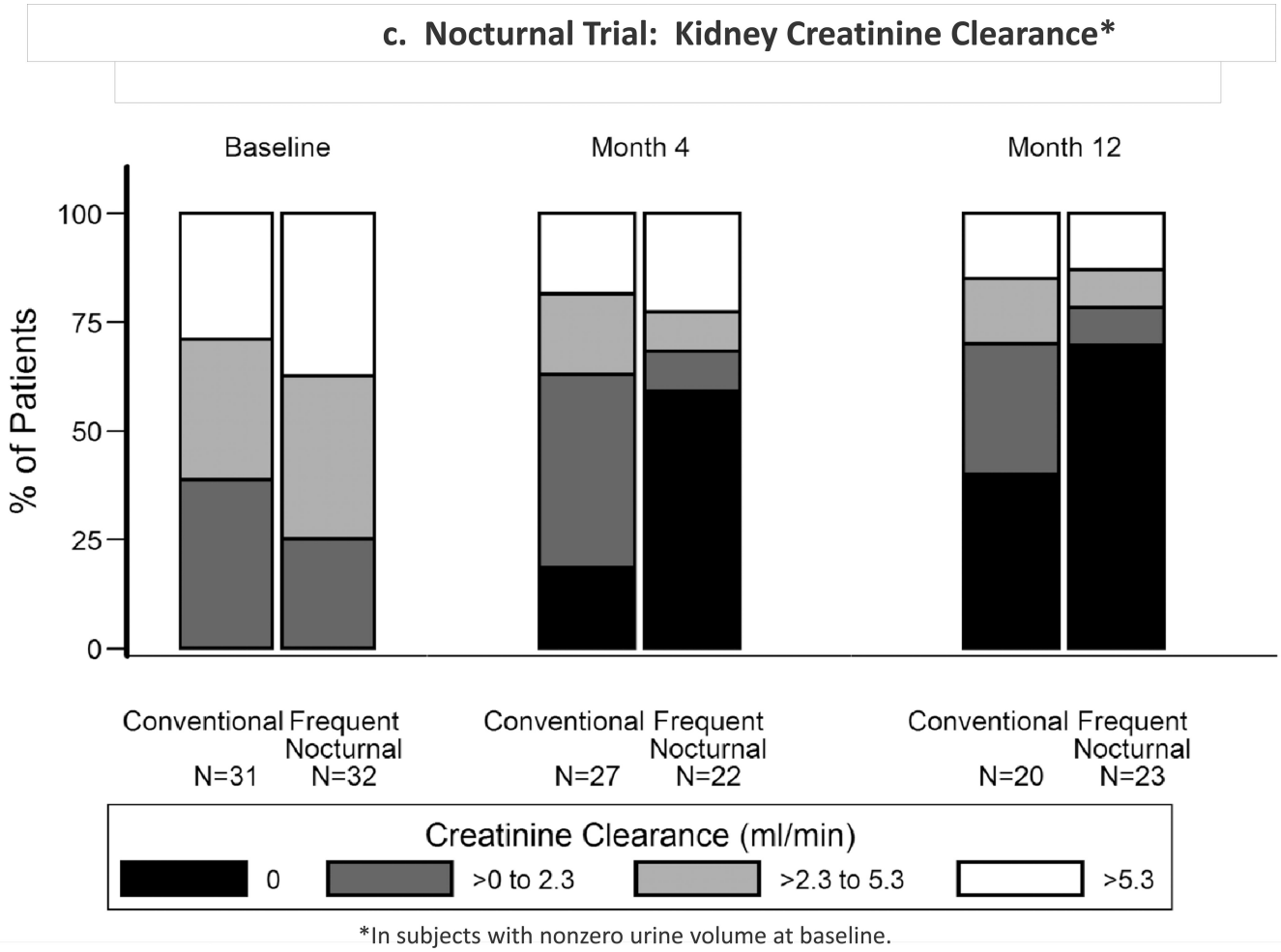
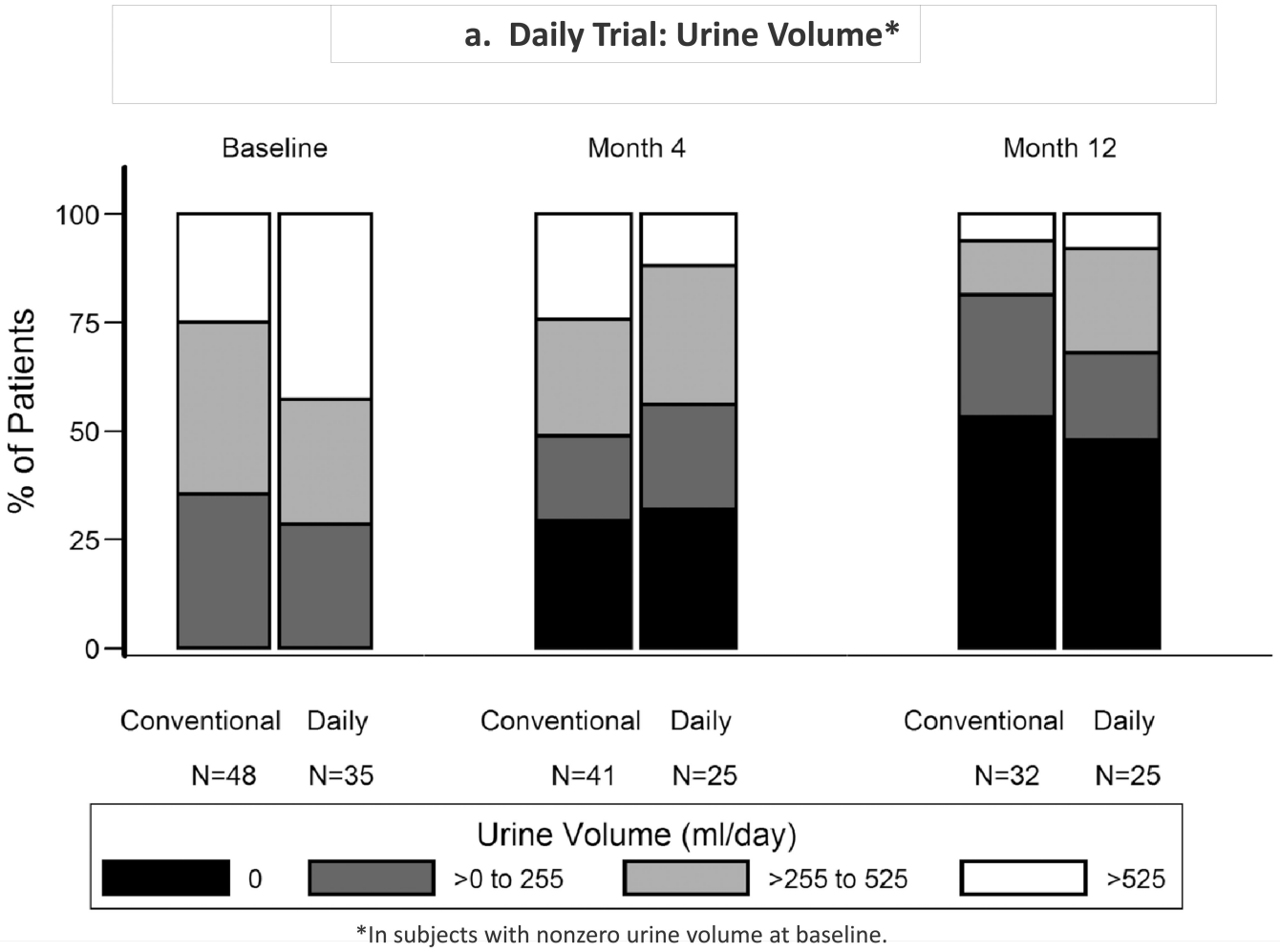
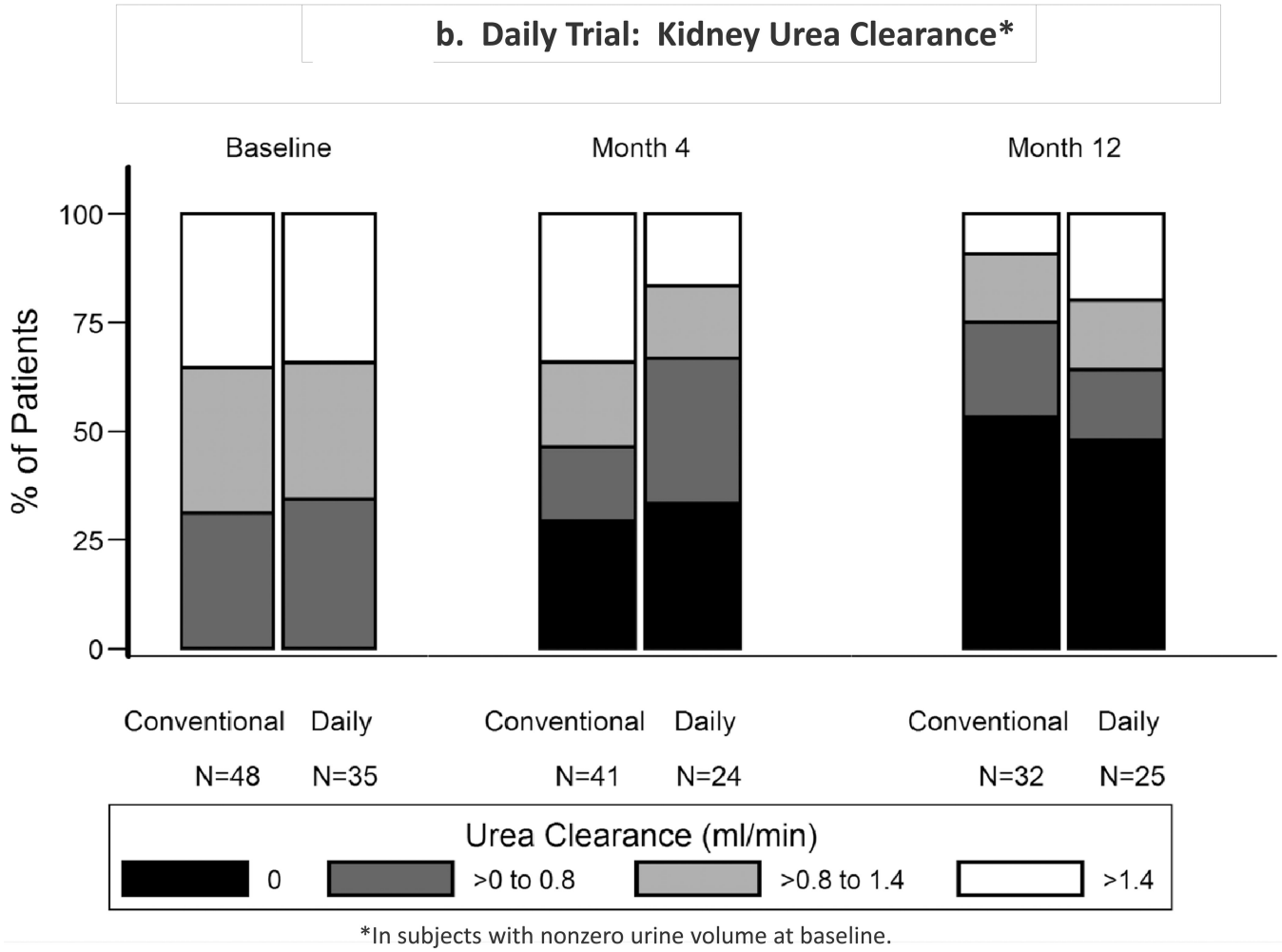


Figure 2.

Nocturnal Trial Subjects with Baseline Nonzero Urine Volume: Time course in level of residual kidney function measured as **(a)** UVol; **(b)** Kru; or **(c)** Krcreat, at baseline, Month 4 and Month 12. The bar graphs depict the proportions of patients falling into the different categories and are provided to describe the outcome distribution. The bar graph ranges represent baseline tertiles (of those with nonzero function at baseline) for each variable. See Table 3 for *P* -values of nonparametric tests comparing the RKF parameters between treatment groups.



*In subjects with nonzero urine volume at baseline.



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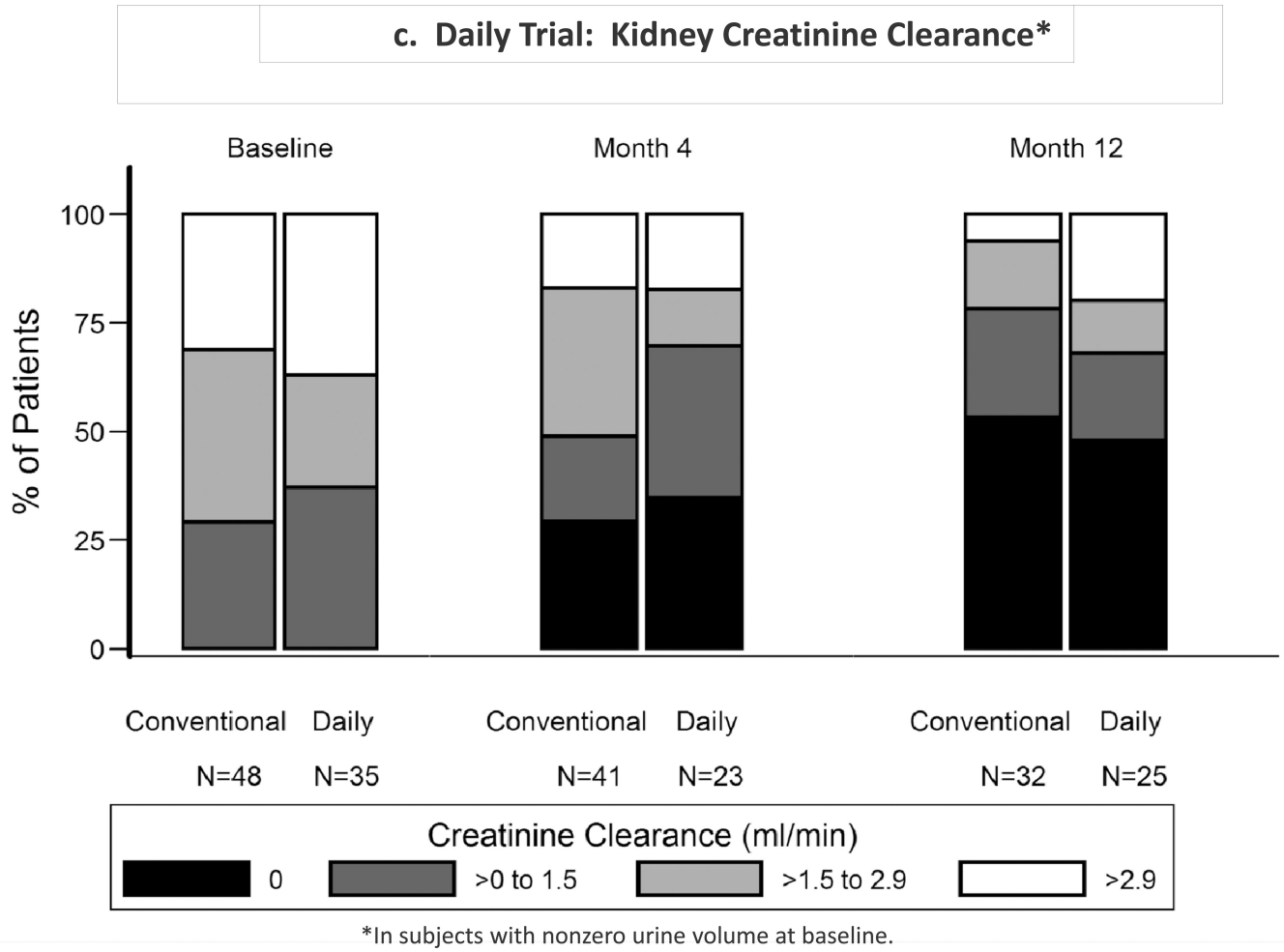

Figure 3.

Daily Trial Subjects with Baseline Nonzero Urine Volume: Time course in level of residual kidney function measured as **(a)** UVol; **(b)** Kru; or **(c)** Krcreat, at baseline, Month 4 and Month 12. The bar graphs depict the proportions of patients falling into the different categories and are provided to describe the outcome distribution. The bar graph ranges represent baseline tertiles (of those with nonzero function at baseline) for each variable. See Table 4 for *P* -values of nonparametric tests comparing the RKF parameters between treatment groups.

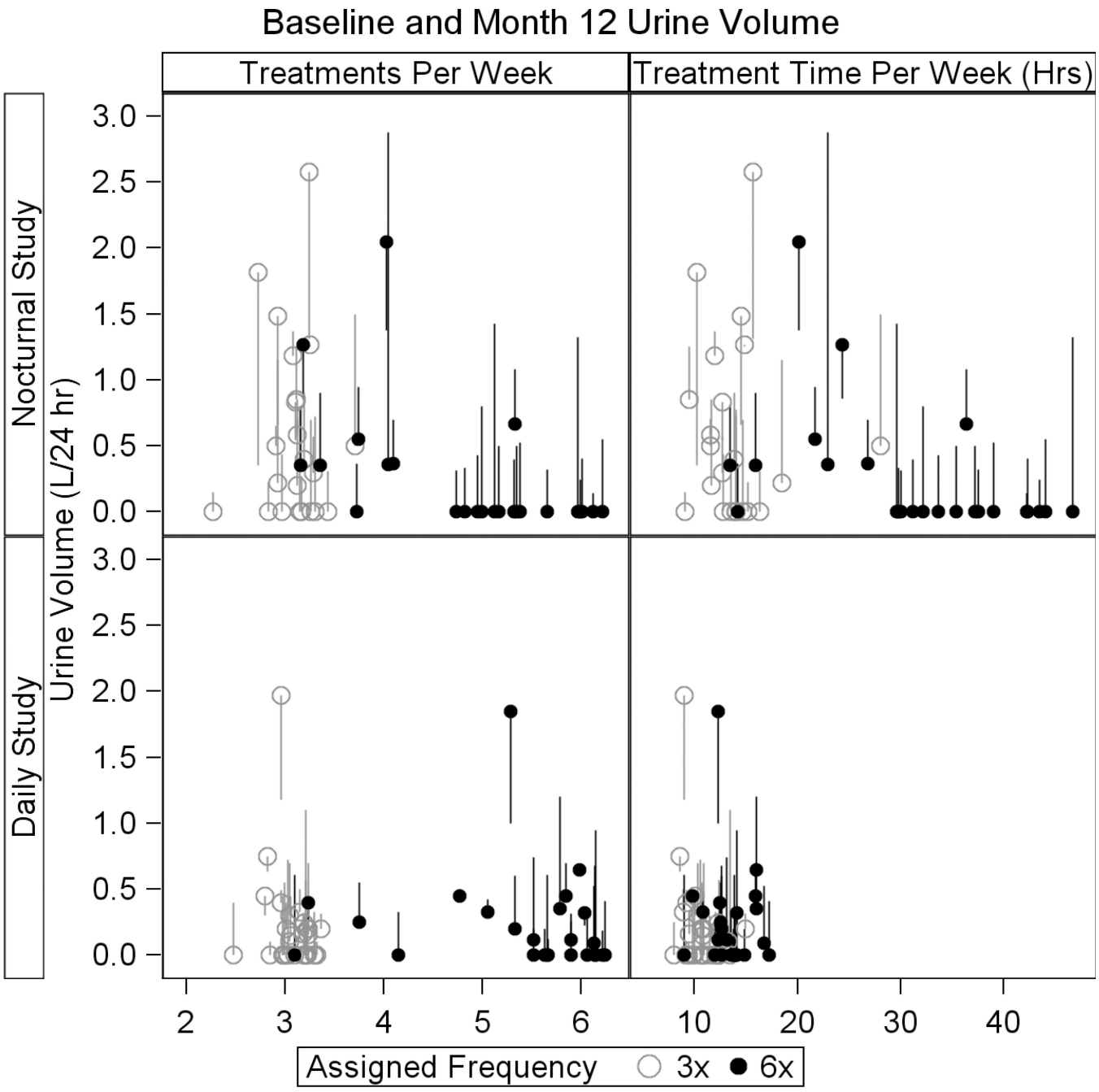

Figure 4.

Baseline and 12-month urine volumes in both trials as a function of average frequency (left panels) and average weekly dialysis times (right panels). Only those participants with nonzero urine volume at baseline were included. The solid circles represent 12-month urine volume for participants randomized to the frequent arm and open circles indicate 12-month urine volume for participants randomized to the control arm. Values of some of the points were shifted laterally slightly to reduce overlap between plot symbols. The endpoint of each

vertical line linking to each circle depicts the baseline urine volume level for that particular subject.

Kidney Int. Author manuscript; available in PMC 2013 December 07.

Table 1

Baseline Characteristics in Patients without and with Urine Output. Nocturnal Trial

	Baseline Urine Volume Group					
	No Urine Output (N = 24)		Urine Volume > 0 (N=63)			
			3X (n=31)		6X (n=32)	
	N	%	N	%	N	%
% Female	10	(41.7)	9	(29.0)	11	(34.4)
% ACE or ARB Use	7	(29.2)	14	(54.2)	9	(28.1)
% Statin Use	9	(37.5)	16	(51.6)	20	(62.5)

	Baseline Urine Volume Group					
	No Urine Output (N=24)		Urine Volume >0 (N=63)			
			3X (n=31)		6X (n=32)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (yrs)	51.7	(14.3)	54.4	(13.4)	52.2	(13.6)
ESRD vintage (years)*	6.1	(8.2)	1.9	(5.1)	3.0	(5.0)
24 hr Urine Volume (L)	0		0.77	(0.45)	0.75	(0.55)
Residual GFR (ml/min)	0		3.20	(2.77)	3.67	(2.51)
Residual Urea Kr (ml/min)	0		2.19	(1.80)	2.37	(1.85)
Residual Creatinine Kr (ml/min)	0		4.22	(3.89)	4.97	(3.32)
LVMI (g/m2)	65.6	(27.8)	71.2	(17.1)	67.7	(20.5)
LVEDV (ml)	154.0	(51.6)	156.1	(46.4)	167.6	(48.7)
Extracellular water (L)	24.8	(6.0)	23.3	(5.7)	24.8	(6.1)
Predialysis BUN (mg/dL)	54.4	(15.6)	54.5	(15.0)	56.0	(21.8)
CO_2 (mmol/L)	23.0	(4.2)	22.6	(3.2)	23.0	(4.1)
Serum Albumin (g/dL)	3.92	(0.52)	3.91	(0.49)	3.90	(0.48)
Predialysis systolic BP (mm Hg)	144.8	(19.8)	155.5	(20.8)	145.8	(13.1)
Predialysis diastolic BP (mm Hg)	78.5	(14.9)	84.8	(12.1)	80.1	(8.9)
Min Intradialysis Sys BP (mm Hg)	115.1	(20.7)	125.9	(18.3)	121.3	(17.1)

* ESRD Vintage: For UVol=0: median 3.16; interquartile range (IQR) 1.13–6.28;
For UVol > 0 and 3X: median 0.38; IQR 0.16-1.30;
For UVol > 0 and 6X: median 0.74; IQR 0.28–3.20.

Table 2

Baseline Characteristics in Patients without and with Urine Output. Daily Trial

	Baseline Urine Volume Group					
	No Urine Output (N=162)		Urine Volume > 0 (N=83)			
			3X (N=48)		6X (N=35)	
	N	%	N	%	N	%
% Female	67	(41.4)	15	(31.3)	12	(34.3)
% ACE or ARB Use	80	(49.4)	24	(50.0)	17	(48.6)
% Statin Use	48	(29.6)	26	(54.2)	15	(42.9)

	Baseline Urine Volume Group					
	No Urine Output (N=162)		Urine Volume > 0 (N=83)			
			3X (N=48) 6X		6X (N=35)	
	Mean	SD	Mean	SD	Mean	SD
Age (yrs)	49.2	(13.7)	54.7	(13.4)	50.0	(14.6)
ESRD vintage (yrs)*	7.4	(6.5)	2.7	(3.6)	2.1	(1.9)
24 hr Urine Volume (L)	0		0.40	(0.25)	0.48	(0.28)
Residual GFR (ml/min)	0		1.83	(1.23)	2.20	(1.77)
Residual Urea Kr (ml/min)	0		1.16	(0.79)	1.27	(0.98)
Residual Creatinine Kr (ml/min)	0		2.50	(1.77)	3.11	(2.82)
LVMI (g/m2)	73.9	(28.2)	71.98	(25.17)	72.61	(22.86)
LVEDV (ml)	174.5	(61.8)	184.5	(64.5)	175.3	(46.5)
Extracellular water (L)	22.3	(4.3)	23.8	(4.6)	23.7	(5.0)
Predialysis BUN (mg/dL)	56.7	(15.6)	62.7	(15.9)	61.1	16.6
CO_2 (mmol/L)	23.8	(3.7)	23.6	(3.4)	23.4	(4.1)
Serum Albumin (g/dL)	3.95	(0.42)	3.93	(0.45)	3.92	(0.35)
Predialysis systolic BP (mm Hg)	145.1	(18.28)	146.5	(17.7)	153.8	(15.5)
Predialysis diastolic BP (mm Hg)	79.5	(11.9)	78.3	(10.4)	83.1	(10.9)
Min Intradialysis Sys BP (mm Hg)	113.6	(19.3)	119.5	(15.0)	123.1	(14.7)

* ESRD Vintage: For UVol=0: median 5.38; interquartile range (IQR) 3.00–9.16;
For UVol > 0 and 3X: median 1.86; IQR 0.58–3.38;
For UVol > 0 and 6X: median 1.48; IQR 0.70–3.09.

Table 3

Changes in Residual Renal Function. Nocturnal Trial Subgroup of 63 Patients with Nonzero Urine Output at Baseline

	Follow-up month 4 (F4)				Follow-up month 12 (F12)			
RKF measure	**(N)**	**(%) Equal to 0**	**(%) Below 1st tertile of RKF measure at baseline***	***P* value****	**(N)**	**(%) Equal to 0**	**(%) Below 1st tertile of RKF measure at baseline***	***P* value****
	3x / 6x	3x / 6x	3x / 6x	**6x vs. 3x**	3x / 6x	3x / 6x	3x / 6x	**6x vs. 3x**
Urine volume /24 hours	28/25	17.9/52.0	50.0/80.0	**0.015**	22 / 24	36.4/66.7	54.5/83.3	**0.06**
Urea Kr	27 / 22	18.5/59.1	63.0/77.3	**0.006**	20 / 23	40.0/69.6	70.0/78.3	**0.003**
Creatinine Kr	27 / 22	18.5/59.1	63.0/68.2	**0.009**	20 / 23	40.0/69.6	70.0/78.3	**0.09**
Average of Urea + Creat Kr	27 / 22	18.5/59.1	59.3/72.7	**0.01**	20 / 23	40.0/68.6	70.0/78.3	**0.008**

* First tertile cutoffs were: Urine volume 500 mL/day; Urea Kr 1.1 mL/min; Creatinine Kr 2.3 mL/min; Average of Urea and Creatinine Kr 1.7 mL/min.

** *P*-values from nonparametric stratified rank sums tests comparing each outcome between the randomized treatment groups at the 4 month and 12 month time points, with stratification by the baseline tertiles of the outcome variable. 3x = subjects randomized to receive conventional 3 times per week dialysis treatments; 6x = subjects randomized to 6 times per week dialysis treatments.

Table 4

Changes in Residual Renal Function. Daily Trial Subgroup of 83 Patients with Nonzero Urine Output at Baseline

	Follow-up month 4 (F4)				Follow-up month 12 (F12)			
RKF measure	**(N)**	**(%) Equal to 0**	**(%) Below 1 st tertile of RKF measure at baseline***	***P* value****	**(N)**	**(%) Equal to 0**	**(%) Below 1 st tertile of RKF measure at baseline***	***P* value****
	3x / 6x	3x / 6x	3x / 6x	**6x vs. 3x**	3x / 6x	3x / 6x	3x / 6x	**6x vs. 3x**
Urine volume /24 hours	41 /25	29.3/32.0	48.8/56.0	**0.14**	32 / 25	53.1/48.0	81.3/68.0	0.99
Urea Kr	41 / 24	29.3/33.3	46.3/66.7	**0.31**	32 / 25	53.1/48.0	75.0/64.0	0.44
Creatinine Kr	41 / 23	29.3/34.8	48.8/69.6	**0.95**	32 / 25	53.1/48.0	78.1/68.0	0.48
Average of Urea + Creat Kr	41 / 23	29.3/34.8	46.3/65.2	**0.59**	32 / 25	53.1/48.0	75.0/68.0	0.42

* First tertile cutoffs were: Urine volume 255 mL/day; Urea Kr 0.8 mL/min; Creatinine Kr 1.5 mL/min; Average of Urea and Creatinine Kr 1.2 mL/min.

** *P*-values from nonparametric stratified rank sums tests compare each outcome between the randomized treatment groups at the 4 month and 12 month time points, with stratification by the baseline tertiles of the outcome variable. 3x = subjects randomized to receive conventional 3 times per week dialysis treatments; 6x = subjects randomized to 6 times per week dialysis treatments.

Table 5

Change in Urinary Volume from Baseline to Month 12 vs. Change in Hypothesized Mediating Factors from Baseline to Month 12

	Spearman R 3X	*P*-value	Spearman R 6X	*P*-value
Nocturnal Trial				
ΔPredialysis Systolic BP (mmHg)	−0.20	0.38	0.02	0.94
ΔPredialysis Diastolic BP (mmHg)	0.21	0.34	0.11	0.60
ΔLowest Intradialytic Systolic BP (mmHg)	0.07	0.76	0.77	0.00
ΔPredialysis BUN (mg/dL)	−0.06	0.78	−0.07	0.74
ΔBIA Extracellular Water (L)	−0.43	0.06	−0.12	0.59
ΔLVEDV (ml)	−0.20	0.36	0.03	0.90
ΔTotal Uf per session (L)	−0.15	0.50	−0.36	0.09
Daily Trial				
ΔPredialysis Systolic BP (mmHg)	0.09	0.61	0.45	0.02
ΔPredialysis Diastolic BP (mmHg)	0.12	0.51	0.33	0.11
ΔLowest Intradialytic Systolic BP (mmHg)	0.06	0.73	0.39	0.05
ΔPredialysis BUN (mg/dL)	0.15	0.42	0.00	0.99
ΔBIA Extracellular Water (L)	−0.21	0.26	0.02	0.93
ΔLVEDV (ml)	0.05	0.80	0.30	0.15
ΔTotal Uf per session (L)	−0.44	0.01	−0.29	0.16

3x = subjects randomized to receive conventional 3 times per week dialysis treatments; 6x = subjects randomized to 6 times per week dialysis treatments. Only patients with nonzero urine volume at baseline were included in this analysis.